HETEROCYCLES, Vol. 75, No. 8, 2008, pp. 1907 - 1911. © The Japan Institute of Heterocyclic Chemistry
Received, 9th March, 2008, Accepted, 15th April, 2008, Published online, 17th April, 2008. COM-08-11384

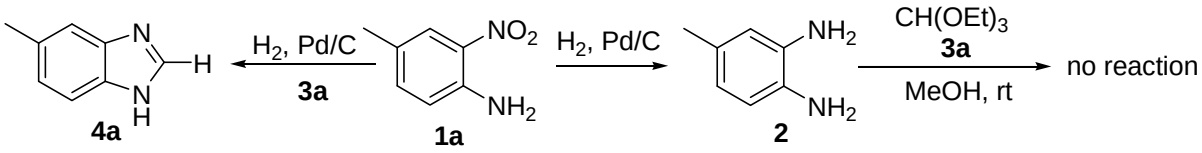
A FACILE ONE-POT SYNTHESIS OF BENZIMIDAZOLES FROM 2-NITROANILINES BY REDUCTIVE CYCLIZATION

Zheng Liu,[1] Haihong Li,[2] Qingjie Zhao,[1] and Jingshan Shen[1,2]*

[1] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555, Zuchongzhi Road, Zhangjiang High-Tech Park, Shanghai 201203, P. R. China
[2] Topharman Shanghai Co., Ltd, 1088, Chuansha Road, Shanghai 201209, P. R. China, email: jsshen@mail.shcnc.ac.cn

Abstract – A facile one-pot process to prepare benzimidazole derivatives is described. Reductive cyclization of a serial of 2-nitroanilines with orthoesters in the presence of Pd/C in methanol at room temperature, which is promoted by a catalytic amount of acetic acid, affords the corresponding benzimidazole derivatives in high yields.

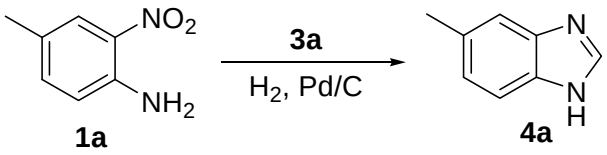
Benzimidazole derivatives are the useful building blocks for Nonpeptide angiotensin II receptor antagonist.[1-3] A number of methods have been developed for preparation of benzimidazoles. For example, benzimidazole derivatives were obtained by microwave-enhanced reaction of *o*-phenylenediamine with carboxylic acids, urea or thiourea, using polyphosphoric acid as a catalyst.[4] 2-Alkylbenzimidazoles were prepared by condensation of *o*-phenylenediamine with aldehydes catalyzed by iodine[5] and Lewis acid[6-8] or oxidized by H_2O_2 in acidic water.[9] Using traditional method, 2-alkyloxybenzimidazole was obtained by catalytic reduction of 2-nitroaniline and subsequently by reaction of the resulting phenylenediamine with orthoester in the hot acidic solution.[10] Microwave-heated one-pot reaction of 2-nitroaniline with carboxylic acid in the presence of reductive agent was reported for synthesis of 2-alkylbenzimidazoles.[11] Though these above methods are very effective to synthesize benzimidazoles, either an excess of acid or heating is required to promote the reactions. In this paper, we report an efficient one-pot synthesis of benzimidazole derivatives under mild conditions. Reductive cyclization of 2-nitroanilines with orthoesters in methanol at room temperature, which is promoted by a catalytic amount of acetic acid, affords the corresponding benzimidazoles in high yields. The facile procedure avoids isolation and purification of the unstable *o*-phenylenediamine and expands application to 2-nitroaniline substrates involving heat or acid-sensitive substituents.



Scheme 1

Initially, synthesis of the benzimidazole **4a** was carried out in two separated steps. Firstly, the *o*-phenylenediamine **2** was readily obtained from the corresponding nitroaniline **1a** by catalytic hydrogenation with 10% Pd/C in high yields. In the second step, we found that no reactions were observed upon treatment of the resulting diamine **2** with orthoesters **3a** in methanol at rt either with or without Pd/C. However, it was noteworthy that cyclization was achieved in the presence of orthoesters during the catalytic hydrogenation of the nitroanilines (Scheme 1).

Table 1. Investigation of reaction conditions [a]



Entry	**3a**/**1a**	Catalyst/**1a**(*C/S*, w/w) [b]	Time (h)	Yield (%) [c]
1	2	1:10	24	-[d]
2	2	1:4	12	94
3	2	1:3	9	93
4	2	Ra-Ni	24	-[d]
5	2	1:10[e]	8	95
6	2	1:10[f]	7	70
7	1	1:4	12	40[g]
8	4	1:4	11	92
9	>10[h]	1:4	8	30

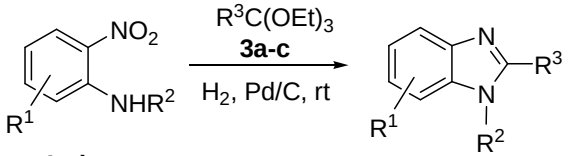
[a] All reactions were performed at room temperature and 1 atm. [b] 10% Pd/C was used as the catalyst unless otherwise stated. [c] Isolated yield. [d] Only the diamine **2** was observed after 24 h based on TLC analysis. [e] A drop of HOAc (ca. 20mg) was added. [f] HOAc was used as solvent. [g] Partially unreacted **1a** was recovered. [h] No solvent was used.

We investigated the conditions of the one-pot synthesis of the benzimidazole **4a**. Experiments were carried out by stirring a mixture of 2-nitroaniline **1a**, triethyl orthoformate **3a** and the catalyst in MeOH under a hydrogen atmosphere at rt. Investigation of reaction conditions is summarized in Table 1. The reaction time depends on the complete conversion of **1a**. According to Table 1, the catalytic amount of 10% Pd/C (*C/S* =1:10 w/w) in reaction system resulted in the only diamine **2** (entry 1). However, when more 10% Pd/C (*C/S* =1:4 w/w) was used as the catalyst, reductive cyclization occurred at rt (entry 2). In addition, increasing the amount of catalyst could reduce the reaction time (entry 3). No desired product **4a** was observed when Ra-Ni was used as the catalyst (entry 4). A catalytic amount of acid could promote the one-pot reaction. Both the reaction time and the amount of Pd/C were reduced. When a drop of HOAc

was added to the reaction of entry 1, the desired product **4a** was obtained in high yield after 8 h (entry 5). However, when HOAc was used as solvent, a few minor impurities were detected (entry 6). Only one equivalent of **3a** in the reaction system resulted in incomplete reaction (entry 7) while 4 equivalents of **3a** did not affect the reaction time and product yield (entry 8). In contrast, using triethyl orthoformate as solvent led to low yield of product (entry 9).

Once the proper conditions were set up, the same procedure[12] was applied to synthesis of various benzimidazoles **4a-k''** from the nitroanilines **1a-l** to investigate the scope and limitations of the one-pot synthetic methodology. Under the optimized reaction conditions, most of the corresponding benzimidazoles were obtained in moderate to good yields (Table 2).

Table 2. Synthesis of benzimidazole derivatives [a]



1a-l **4a-k"**

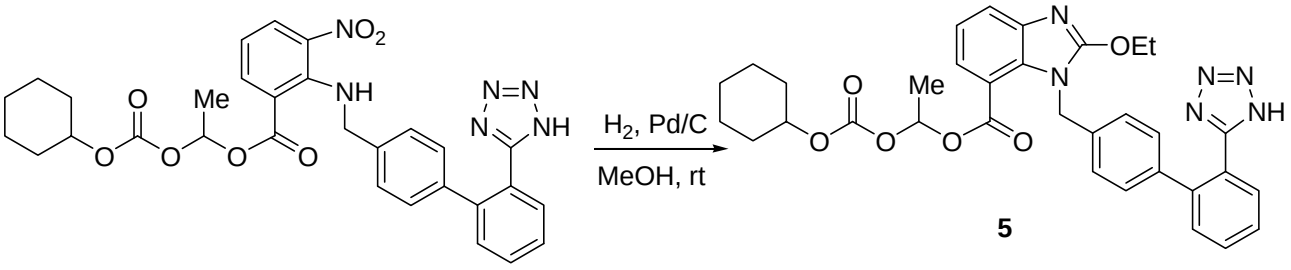
Entry	Substrates	R^1	R^2	R^3	Product	Yield (%)[b]
1	**1a+3a**	4-Me	H	H	**4a**	95
2	**1a+3b**	4-Me	H	OEt	**4a'**	93
3	**1a+3c**	4-Me	H	Me	**4a"**	94
4	**1b+3a**	6-CO_2Et	H	H	**4b**	95
5	**1b+3b**	6-CO_2Et	H	OEt	**4b'**	93
6	**1b+3c**	6-CO_2Et	H	Me	**4b"**	93
7	**1c+3a**	6-CO_2H	H	H	**4c**	90
8	**1c+3b**	6-CO_2H	H	OEt	**4c'**	88
9	**1c+3c**	6-CO_2H	H	Me	**4c"**	87
10	**1d+3a**	H	H	H	**4d**	93
11	**1d+3b**	H	H	OEt	**4d'**	91
12	**1d+3c**	H	H	Me	**4d"**	95
13	**1e+3a**	H	Me	H	**4e**	78
14	**1e+3b**	H	Me	OEt	**4e'**	75
15	**1e+3c**	H	Me	Me	**4e"**	80
16	**1f+3a**	6-CO_2Et	Boc	H	**4b**[c]	52
17	**1f+3b**	6-CO_2Et	Boc	OEt	**4b'**[c]	55
18	**1f+3c**	6-CO_2Et	Boc	Me	**4b"**[c]	45
19	**1g+3a**	4-Cl	H	H	**4f**	-[d]
20	**1g+3b**	4-Cl	H	OEt	**4f'**	-[d]
21	**1g+3c**	4-Cl	H	Me	**4f"**	-[d]
22	**1h+3a**	5-CF_3	H	H	**4g**	96
23	**1h+3b**	5-CF_3	H	OEt	**4g'**	96
24	**1h+3c**	5-CF_3	H	Me	**4g"**	94
25	**1i+3a**	4,5-dimethyl	H	H	**4h**	94
26	**1i+3b**	4,5-dimethyl	H	OEt	**4h'**	94
27	**1i+3c**	4,5-dimethyl	H	Me	**4h"**	92
28	**1j+3a**	4-CN	H	H	**4i**	88
29	**1j+3b**	4-CN	H	OEt	**4i'**	90
30	**1j+3c**	4-CN	H	Me	**4i"**	90

Entry	Substrates	R^1	R^2	R^3	Product	Yield (%)[b]
31	**1k+3a**	5-F	H	H	**4j**	93
32	**1k+3b**	5-F	H	OEt	**4j'**	94
33	**1k+3c**	5-F	H	Me	**4j"**	94
34	**1l+3a**	4-OH	H	H	**4k**	75
35	**1l+3b**	4-OH	H	OEt	**4k'**	78
36	**1l+3c**	4-OH	H	Me	**4k"**	75

[a] All reactions were performed overnight by catalytic hydrogenation using 10% Pd/C (*C/S* =1:10 w/w) as catalyst at room temperature and 1 atm with a **1**: **3** molar ratio = 1:2 and a drop of HOAc inMeOH. [b] Isolated via recrystallization or column chromatography. [c] The reaction was complete after 24 h and the Boc group was removed. [d] The reaction was messy after 12 h.

The substituents on the aromatic ring have shown effects on the formation of the target product. The aromatic ring bearing methyl, ester, carboxyl group, hydrogen, trifluoromethyl, dimethyl, nitrile and fluoro groups with no substituent on the amino group (**1a-d, 1h-k**) proceeded in high yields of 87-96% (entries 1-12, 22-33). Whether orthoester **3a**, **3b** or **3c** was chosen as reactive reagent did not affect the product yields. Nitroaniline **1e** with substituents on amino group led to lower yield than *N*-unsubstituted nitroanilines (entries 13-15). The reaction of the chloro-substituted nitroanilines **1g** became messy. The dechloro products and a minor amount of products were detected (entries 19-21). The benzimidazoles **4k-k"** were obtained from nitroaniline **1l** possessing hydroxyl group in moderate yields (entries 22-24). Comparing to the unprotected aniline **1b**, the presence of Boc group on aromatic amine **1f** resulted in the long reaction time and low yields (entries 16-18). It was suggested that the steric hinderance and low basicity of carbamate inhibited cyclization. Though the Boc group can be removed at high temperature[13] or under acidic conditions,[14] we found the Boc group on the nitroaniline **1f** was partially removed. The deprotected diamine derived from **1f** was also detected in the reaction mixture during the reductive cyclization.

In conclusion, we described a facile one-pot process to produce benzimidazoles from 2-nitroanilines and orthoesters by reductive cyclization in methanol at rt. The attractive features of this process are facile procedure, mild reaction conditions, expansion of application to heat and acid-sensitive 2-nitroanilines and high yield of product. Further efforts to optimize the process of candesartan cilexetil **5**[2,15,16] using this efficient one-pot method are now in progress (Scheme 2) and will be reported in near future.



Scheme 2

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12. **Typical procedure for one-pot synthesis of benzimidazole derivatives**: To a solution of the appropriate 2-nitroaniline **1** (2.0 mmol, 1 equiv), orthoester **3a**, **3b** or **3c** (4.0 mmol, 2 equiv) and a drop of HOAc in MeOH (10 mL) was added 10% Pd/C (*C/S* =1:10 w/w). The reaction was stirred overnight at rt under a hydrogen atmosphere (1 atm). After completion, the reaction mixture was filtrated and evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel or recrystallization to afford the pure benzimidazole **4**.
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